OIPE
APR 22 2002
PATENT & TRADEMARK OFFICE


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ATGTCCATGA ACTGCTGAGT GGATAAACAG CACGGGATAT CTCTGTCTAA          -96
AGGAATATTA CTACACCAGG AAAAGGACAC ATTCGACAAC AGGAAAGGAG          -46
CCTGTCACAG AAAACCACAG TGTCCTGTGC ATGTGACATT TCGCC                -1

ATG GGA AAC AAC TGT TAC AAC GTG GTG GTC ATT GTG CTG CTG CTA      45
Met Gly Asn Asn Cys Tyr Asn Val Val Val Ile Val Leu Leu Leu

GTG GGC TGT GAG AAG GTG GGA GCC GTG CAG AAC TCC TGT GAT AAC     90
Val Gly Cys Glu Lys Val Gly Ala Val Gln Asn Ser Cys Asp Asn

TGT CAG CCT GGT ACT TTC TGC AGA AAA TAC AAT CCA GTC TGC AAG     135
Cys Gln Pro Gly Thr Phe Cys Arg Lys Tyr Asn Pro Val Cys Lys
                          H4-1BB FI

AGC TGC CCT CCA AGT ACC TTC TCC AGC ATA GGT GGA CAG CCG AAC     180
Ser Cys Pro Pro Ser Thr Phe Ser Ser Ile Gly Gly Gln Pro Asn
                          H4-1BB FII

TGT AAC ATC TGC AGA GTG TGT GCA GGC TAT TTC AGG TTC AAG AAG     225
Cys Asn Ile Cys Arg Val Cys Ala Gly Tyr Phe Arg Phe Lys Lys

TTT TGC TCC TCT ACC CAC AAC GCG GAG TGT GAG TGC ATT GAA GGA     270
Phe Cys Ser Ser Thr His Asn Ala Glu Cys Glu Cys Ile Glu Gly

TTC CAT TGC TTG GGG CCA CAG TGC ACC AGA TGT GAA AAG GAC TGC     315
Phe His Cys Leu Gly Pro Gln Cys Thr Arg Cys Glu Lys Asp Cys

AGG CCT GGC CAG GAG CTA ACG AAG CAG GGT TGC AAA ACC TGT AGC     360
Arg Pro Gly Gln Glu Leu Thr Lys Gln Gly Cys Lys Thr Cys Ser
                                        H4-1BB RI

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Leu Gly Thr Phe Asn Asp Gln Asn Gly Thr Gly Val Cys Arg Pro
          H4-1BB RII

TGG ACG AAC TGC TCT CTA GAC GGA AGG TCT GTG CTT AAG ACC GGG     450
Trp Thr Asn Cys Ser Leu Asp Gly Arg Ser Val Leu Lys Thr Gly

ACC ACG GAG AAG GAC GTG GTG TGT GGA CCC CCT GTG GTG AGC TTC     495
Thr Thr Glu Lys Asp Val Val Cys Gly Pro Pro Val Val Ser Phe

TCT CCC AGT ACC ACC ATT TCT GTG ACT CCA GAG GGA GGA CCA GGA     540
Ser Pro Ser Thr Thr Ile Ser Val Thr Pro Glu Gly Gly Pro Gly

GGG CAC TCC TTG CAG GTC CTT ACC TTG TTC CTG GCG CTG ACA TCG     585
Gly His Ser Leu Gln Val Leu Thr Leu Phe Leu Ala Leu Thr Ser

GCT TTG CTG CTG GCC CTG ATC TTC ATT ACT CTC CTG TTC TCT GTG     630
Ala Leu Leu Leu Ala Leu Ile Phe Ile Thr Leu Leu Phe Ser Val
```

Fig. 1

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CTC AAA TGG ATC AGG AAA AAA TTC CCC CAC ATA TTC AAG CAA CCA     675
Leu Lys Trp Ile Arg Lys Lys Phe Pro His Ile Phe Lys Gln Pro

TTT AAG AAG ACC ACT GGA GCA GCT CAA GAG GAA GAT GCT TGT AGC     720
Phe Lys Lys Thr Thr Gly Ala Ala Gln Glu Glu Asp Ala Cys Ser

TGC CGA TGT CCA CAG GAA GAA GAA GGA GGA GGA GGA GGC TAT GAG     765
Cys Arg Cys Pro Gln Glu Glu Glu Gly Gly Gly Gly Gly Tyr Glu

CTG TGA                                                        771
Leu ---


TGTACTATCC TAGGAGATGT GTGGGCCGAA ACCGAGAAGC ACTAGGACCC          821
CACCATCCTG TGGAACAGCA CAAGCAACCC CACCACCCTG TTCTTACACA          871
TCATCCTAGA TGATGTGTGG GCGCGCACCT CATCCAAGTC TCTTCTAACG          921
CTAACATATT TGTCTTTACC TTTTTTAAAT CTTTTTTTAA ATTTAAATTT          971
TATGTGTGTG AGTGTTTTGC CTGCCTGTAT GCACACGTGT GTGTGTGTGT         1021
GTGTGTGACA CTCCTGATGC CTGAGGAGGT CAGAAGACAA AGGGTTGGTT         1071
CCATAAGAAC TGGAGTTATG GATGGCTGTG AGCCGGNNNG ATAGGTCGGG         1121
ACGGAGACCT GTCTTCTTAT TTTAACGTGA CTGTATAATA AAAAAAAAAT         1171
GATATTTCGG GAATTGTAGA GATTGTCCTG ACACCCTTCT AGTTAATGAT         1221
CTAAGAGGAA TTGTTGATAC GTAGTATACT GTATATGTGT ATGTATATGT         1271
ATATGTATAT ATAAGACTCT TTTACTGTCA AAGTCAACCT AGAGTGTCTG         1321
GTTACCAGGT CAATTTTATT GGACATTTTA CGTCACACAC ACACACACAC         1371
ACACACACAC ACGTTTATAC TACGTACTGT TATCGGTATT CTACGTCATA         1421
TAATGGGATA GGGTAAAAGG AAACCAAAGA GTGAGTGATA TTATTGTGGA         1471
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GTCTAAAACT CCCCTTAGAA GTCTCGTCAA GTTCCCGGAC GAAGAGGACA         1571
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TCGTGACACT CCACCCCTTG TGGACACTTG AGTGTCATCC TTGCGCCGGA         1671
AGGTCAGGTG GTACCCGTCT GTAGGGGCGG GGAGACAGAG CCGCGGGGGA         1721
GCTACGAGAA TCGACTCACA GGGCGCCCCG GGCTTCGCAA ATGAAACTTT         1771
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TTACAAAAGT AATTAGTTCT TGCTTTCAGC CTCCAAGCTT CTGCTAGTCT         2021
ATGGCAGCAT CAAGGCTGGT ATTTGCTACG GCTGACCGCT ACGCCGCCGC         2071
AATAAGGGTA CTGGGCGGCC CGTCGAAGGC CCTTTGGTTT CAGAAACCCA         2121
AGGCCCCCCT CATACCAACG TTTCGACTTT GATTCTTGCC GGTACGTGGT         2171
GGTGGGTGCC TTAGCTCTTT CTCGATAGTT AGAC                          2205
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Fig. 1 Cont'd

human homologue of mouse 4-1bb

h4-1bb Length 838

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  1  AATCAGCTTT GCTAGTATCA TACCTGTGCC AGATTTCATC ATGGGAAACA
 51  GCTGTTACAA CATAGTAGCC ACTCTGTTGC TGGTCCTCAA CTTTGAGAGG
101  ACAAGATCAT TGCAGGATCC TTGTAGTAAC TGCCCAGCTG GTACATTCTG
151  TGATAATAAC AGGAATCAGA TTTGCAGTCC CTGTCCTCCA AATAGTTTCT
201  CCAGCGCAGG TGGACAAAGG ACCTGTGACA TATGCAGGCA GTGTAAAGGT
251  GTTTTCAGGA CCAGGAAGGA GTGTTCCTCC ACCAGCAATG CAGAGTGTGA
301  CTGCACTCCA GGGTTTCACT GCCTGGGGGC AGGATGCAGC ATGTGTGAAC
351  AGGATTGTAA ACAAGGTCAA GAACTGACAA AAAAAGGTTG TAAAGACTGT
401  TGCTTTGGGA CATTTAACGA TCAGAAACGT GGCATCTGTC GACCCTGGAC
451  AAACTGTTCT TTGGATGGAA AGTCTGTGCT TGTGAATGGG ACGAAGGAGA
501  GGGACGTGGT CTGTGGACCA TCTCCAGCTG ACCTCTCTCC GGGAGCATCC
551  TCTGTGACCC CGCCTGCCCC TGCGAGAGAG CCAGGACACT CTCCGCAGAT
601  CATCTCCTTC TTTCTTGCGC TGACGTCGAC TGCGTTGCTC TTCCTGCTGT
651  TCTTCCTCAC GCTCCGTTTC TCTGTTGTTA AACGGGGCAG AAAGAAACTC
701  CTGTATATAT TCAAACAACC ATTTATGAGA CCAGTACAAA CTACTCAAGA
751  GGAAGATGGC TGTAGCTGCC GATTTCCAGA AGAAGAAGAA GGAGGATGTG
801  AACTGTGAAA TGGAAGTCAA TAGGGCTGTT GGGACTTT
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Fig.2A

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  1  MGNSCYNIVA TLLLVLNFER TRSLQDPCSN CPAGTFCDNN RNQICSPCPP
 51  NSFSSAGGQR TCDICRQCKG VFRTRKECSS TSNAECDCTP GFHCLGAGCS
101  MCEQDCKQGQ ELTKKGCKDC CFGTFNDQKR GICRPWTNCS LDGKSVLVNG
151  TKERDVVCGP SPADLSPGAS SVTPPAPARE PGHSPQIISF FLALTSTALL
201  FLLFFLTLRF SVVKRGRKKL LYIFKQPFMR PVQTTQEEDG CSCRFPEEEE
251  GGCEL
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Fig.2B

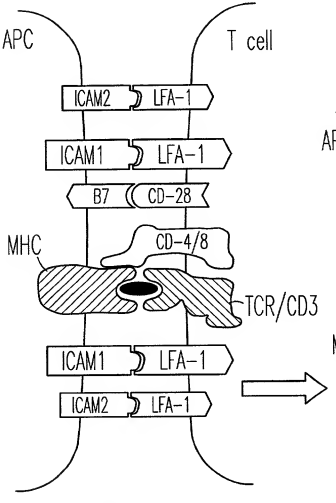
APC
T cell
ICAM2
LFA-1
ICAM1
LFA-1
B7
CD-28
MHC
CD-4/8
TCR/CD3
ICAM1
LFA-1
ICAM2
LFA-1
COGNITIVE PHASE
EARLY ACTIVATION

Fig. 3a

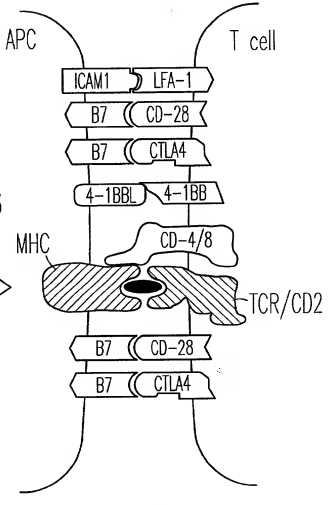
APC
T cell
ICAM1
LFA-1
B7
CD-28
B7
CTLA4
4-1BBL
4-1BB
MHC
CD-4/8
TCR/CD2
B7
CD-28
B7
CTLA4
PROLIFERATION
CLONAL EXPANSION
LATE ACTIVATION

Fig. 3b

NORMAL T CELL ACTIVATION PATHWAY

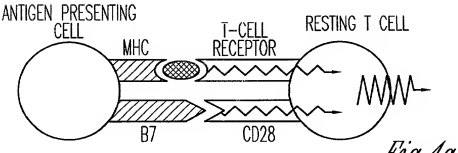

Fig. 4a

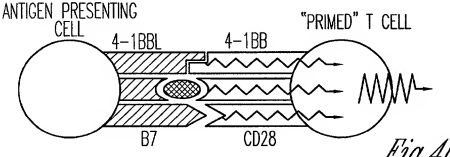

Fig. 4b

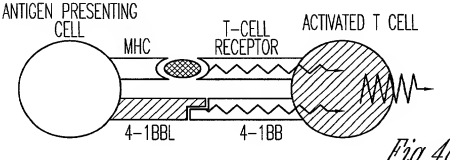

Fig. 4c

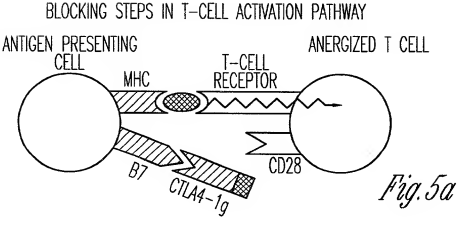

Fig. 5a

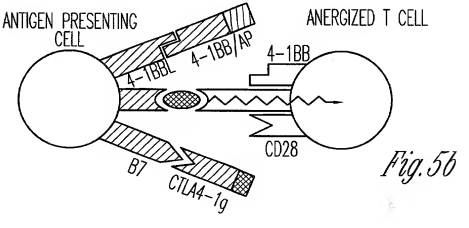

Fig. 5b

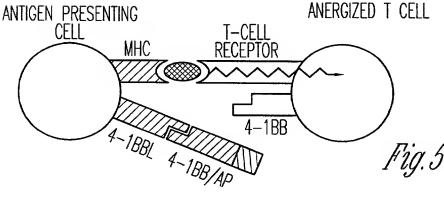

Fig. 5c